(d) repeating (a)-(c) at least once.

REMARKS

Applicants thank Examiner Chakrabarti and his supervisor Examiner Fredman for conducting separate telephone interviews with the undersigned on March 14 and March 18 respectively. Examiner Chakrabati maintained his position from the last office action. His position was, "although Skiena does not teach an array of probes wherein the sequence of the target nucleic acid is a variant of the reference sequence," Futreal provides sufficient motivation to modify the teachings of Skiena in this regard. Examiner Fredman, however, took a somewhat different view, which was that the claims could be read more broadly. Examiner Fredman indicated that amendment of the claims to exclude complete arrays might serve to distinguish the outstanding rejection. Examiner Fredman acknowledged that he understood applicants were not intending to claim complete arrays but felt that this had to be made more explicit in the claims.

In light of these comments, applicants have amended the independent claims to specify that the arrays are not complete arrays containing all probes of a given length. Support for the amendment to claims 1 and 15 is provided by e.g., p. 10, lines 17-18. Although it is acknowledged that the present case is after final, it is submitted that entry of the amendment is nevertheless proper to either place the case in conditions for allowance or simply issues for appeal for the following reasons. First, there is no question that the amendment is expressly supported by the specification and hence no question of new matter. Second, the amendment merely makes explicit the interpretation of the claims that was previously intended, and which appears to have been understood by Examiner Chakrabati in conducting examination. Such is evident from Examiner Chakrabati's comment that "Skiena does not teach an array of proves wherein the sequence of the target nucleic acid is a variant of the reference sequence" (final office action at p. 2). Because the amendment does not change the interpretation of the Examiner in conducting examination, no new search is required. Third, it is submitted

that entry of the amendment will put the case into condition for allowance or at least simplify issues for appeal. As noted above, Examiner Fredman's preliminary view was that the amendment would serve to distinguish the outstanding rejection. Moreover, even if this view does not hold on further consideration by the Examiners, the amendment would simplify issues for appeal in removing a technical issue involving interpretation of the claims when as Examiner Fredman acknowledged, it is clear what applicants intended the claims to mean.

In light of these comments, Examiner's Chakrabati and Fredman are requested to reconsider the arguments made with the last response, and briefly summarized below. In brief, Skiena does not disclose designing an array of probes to comprise a probe set complementary to a known reference sequence. Rather, Skiena's initial array is a universal sequencing chip containing all probes of a given length (col. 2, lines 23-24). By definition, such an array contains all probes of a given length, and is not designed with respect to a reference sequence.

The Examiner relies on Futreal to establish that target sequences that are variants of a reference sequence are known to exist and it is useful to analyzed them with probe based assays. However, merely performing Skiena's method with a target sequence that happens to be a variant of a known reference sequence does not remedy the deficiency in Skiena's design of an array.

Not only would one have to perform Skiena's method with a target sequence that is a variant of a known reference sequence, one would at the very least have to discard Skiena's own strategy of starting with a universal sequence array containing all probes of a given length in favor of designing an array to comprise a set of probes having complementarity to the known reference sequence. To do so would forfeit the utility of Skiena's own method for an analyzing any kind of target sequence. Moreover, the remaining steps in Skiena method which are intended for analyzing a target sequence without any prior knowledge as to its identity would seem unnecessarily complex for the simpler task of analyzing a variant of a known sequence. The Futreal reference merely indicates the well-known fact that target sequences that are variants of

known reference sequences exist; it does not provide any suggestion to modify the strategy for analyzing target sequences proposed by Skiena, and particularly not in a way that forfeits the principal advantage of Skiena's method

Applicants also previously pointed out that Skiena does not discloses 'estimating," or "reestimating" a target sequence, much less "reestimating" the sequence until it remains constant between successive cycles. The Examiner appears to take the view that simply determining a set of hybridizing oligonucleotides itself constitutes "estimating the sequence of a target," under a broad interpretation of the claims which the Examiner feels entitled to make during prosecution. In response, applicants submit that the Examiner is not merely interpreting the claims broadly, but effectively reading out explicitly recited claim steps. The present claims recite separate steps of "determining the relative hybridization of the probes to the target nucleic acid," and "estimating the sequence of the target nucleic acid from the relative hybridization of the probes." Thus, to view "determining the relative hybridization of probes" as being equivalent to estimating a sequence effectively reads out the step of "estimating the sequence" from the claim. Accordingly, Applicants maintain that Skiena does not teach 'estimating," or "reestimating" a target sequence, much less "reestimating" the sequence until it remains constant between successive cycles.

The distinction based on Skiena's lack of disclosure of "estimating" a sequence is all the more evident in dependent claim 13. This claim recites that the step of "estimating" includes "repeating (a) and (b) until each nucleotide of interest in the sequence of the target nucleic acid has been estimated." In Skiena's initial iterations of his method, he does not disclose estimating a target sequence but rather identifies a subset of hybridizing probes, which is used to design a second set of probes. In the final step of Skiena's method he does not estimate a target sequence, but rather determines the sequence uniquely. In Skiena's view at least, the determined sequence is correct and not an estimated, much less a reestimated sequence (col. 7, lines 12-15). Therefore, Skiena does not estimate each nucleotide of interest in a target sequence, as recited in claim 13.

For these reasons, as well as the reasons in the response of November 29, 2001, it is submitted the rejection should be withdrawn.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claim 1 was amended as follows:

1. (Amended) A method of analyzing a target nucleic acid, comprising:

(a) designing an array of probes to comprise a probe set comprising probes complementary to a known reference sequence;

(b) hybridizing the target nucleic acid to the array of probes, wherein the sequence of the target nucleic acid is a variant of the reference sequence and provided the probe array does not contain every possible probe sequence of a given length;

(c) determining the relative hybridization of the probes to the target nucleic acid,

(d) estimating the sequence of the target nucleic acid from the relative hybridization of the probes;

(e) providing a further array of probes comprising a probe set comprising probes complementary to the estimated sequence of the target nucleic acid and provided the further probe array does not contain every possible probe sequence of a given length;

(f) hybridizing the target nucleic acid to the further array of probes;

(g) determining the relative hybridization of the probes to the target nucleic acid;

(h) reestimating the sequence of the target nucleic acid from the relative hybridization of the probes.

Claim 15 was amended as follows:

15. (Amended) A method of analyzing a target nucleic acid, comprising:

(a) designing an array of probes to be complementary to an estimated sequence of the target nucleic acid provided the array does not contain every possible probe sequence of a given length,

(b) hybridizing the array of probes to the target nucleic acid;

(c) determining a reestimated sequence of the target nucleic acid from the hybridization pattern of the array to the target nucleic acid sequence to; and

(d) repeating (a)-(c) at least once.